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ORIGINAL PAPER

Problem of nonresponse to allergen immunotherapy

Problem braku odpowiedzi na immunoterapię alergenową

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ABSTRACT

Introduction: Allergen immunotherapy (AIT) is very important and effective and reduces medication use in patients with allergic rhinitis. However, some patients have no response to AIT.
Aim: To explore the problem of nonresponding patients after AIT.
Material and methods: This retrospective randomized observational study included 1056 patients with allergic rhinitis who underwent subcutaneous injection allergen immunotherapy (SCIT). Patients who received SCIT to one of the following allergens: grass pollen, birch, trees, mugwort, house dust mites, *Alternaria* or cat were analyzed according to the inclusion criterion of ≥ 20% improvement in all monitored parameters. There were symptoms and medication score, rhinitis symptom score and serum allergen-specific IgE and IgG4.
Results: A total of 806 (76.3%) patients met the criterion of 20% or greater improvement after SCIT. The greatest effectiveness was obtained in patients receiving SCIT to grass pollen (293 participants; 83.2%), birch (82; 81.2%) and house dust mites (255; 76.4%). Statistically significant predictors of an improved AIT outcome in the multivariate analysis were SCIT to grass pollen (OR = 2.34, $p = 0.035$), SCIT to birch (OR = 2.25, $p = 0.021$) and the presence of only intermittent allergic rhinitis before SCIT (OR = 2.05, $p = 0.039$). Patients who received SCIT to mugwort, *Alternaria* or cat had weak response results especially in long-term observations.
Conclusions: The best predictors to obtain good responsiveness to SCIT are the presence of intermittent allergic rhinitis to grass or birch pollen. Patients with allergies to mugwort, *Alternaria* and cat with a prolonged duration of persistent allergic rhinitis dominated in the group of nonresponders to SCIT.

KEY WORDS

immunotherapy, allergy, IgE, rhinitis.

STRESZCZENIE

Wprowadzenie: Immunoterapia alergenowa (AIT) jest metodą bardzo ważną, skuteczną i redukującą konieczność używania leków objawowych u pacjentów z alergicznym nieżytem nosa. Niestety część chorych nie odpowiada na tego typu leczenie.
Cel pracy: Próba oceny problemu braku odpowiedzi na AIT u chorych poddanych immunoterapii.
Materiał i metody: W badaniu obserwacyjnym, retrospektywnym z elementami randomizacji poddano analizie 1056 chorych z alergicznym nieżytem nosa, u których stosowano iniekcyjną immunoterapię alergenową (SCIT). W grupie badanej znaleźli się chorzy odczulani na jedną z następujących grup alergenów: trawy,

brzoza, drzewa, bylica, roztocze kurzu domowego, *Alternaria* albo sierść kota. Oceniano kryterium co najmniej 20-procentowej poprawy we wszystkich analizowanych parametrach, takich jak wskaźnik zużycia leków, objawy nieżytu nosa, stężenie alergenowo swoistej IgE oraz odpowiedniego IgG4.

Wyniki: Osiemset sześciu (76,3%) pacjentów uzyskało kryterium poprawy o co najmniej 20% po SCIT. Największy efekt obserwowano u chorych odczulanych na trawy (293 badanych; 83,2%), brzozę (82; 81,2%) i roztocze kurzu domowego (255; 76,4%). Istotnym statystycznie predyktorem dobrej odpowiedzi na SCIT w analizie wielowymiarowej były: SCIT na trawy (OR = 2,34, p = 0,035), SCIT na brzozę (OR = 2,25, p = 0,021) oraz obecność tylko sporadycznego alergicznego nieżytu nosa przed SCIT (OR = 2,05, p = 0,0039). Pacjenci odczulani na bylicę, *Alternaria* lub kota mieli słabą odpowiedź na leczenie, zwłaszcza w długofalowej obserwacji.

Wnioski: Najlepszym predyktorem uzyskania dobrej skuteczności SCIT jest obecność sporadycznego alergicznego nieżytu nosa z towarzyszącym uczuleniem na trawy lub brzozę przed rozpoczęciem immunoterapii. Pacjenci z alergią na bylicę, *Alternaria* lub kota, a także z przewlekłym długoletnim nieżytem nosa przeważali w grupie chorych ze słabą odpowiedzią na immunoterapię.

SŁOWA KLUCZOWE

immunoterapia, alergia, IgE, nieżyt nosa.

ADDRESS FOR CORRESPONDENCE

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INTRODUCTION

Chronic rhinitis is a significant problem worldwide, with approximately 8–40% of people affected [1]. Allergen immunotherapy (AIT) is an important tool in the treatment of allergic rhinitis [2]. AIT offers a safe and effective treatment method, especially for mild and severe, intermittent or persistent allergic rhinitis with concomitant allergies to pollens, house dust mites and other allergens. Several studies have confirmed the efficacy of AIT [2]. There have been many trials and meta-analyses that recommend this treatment for patients who meet the inclusion criteria [2–6]. Recently, guidelines have highlighted the pivotal role of AIT for the etiological treatment of allergic rhinoconjunctivitis [3].

However, despite patients with allergic rhinitis meeting the requirements for AIT, several of them still experience weak therapeutic effects relative to their expectations for the treatment. Different AIT protocols, different allergens that patients are desensitized to and many other factors can determine the effectiveness of immunotherapy. However, the possible factors leading to the reduced efficacy of AIT have only partially been addressed. Additionally, the prolonged effect of AIT has rarely been investigated [4].

AIM

The aim of the study was to explore factors that could influence the effect or lack of effect after injection AIT (SCIT) to common inhaled allergens.

MATERIAL AND METHODS

This was a retrospective observational study based on databases of patients who received a course of SCIT. The effect of SCIT was analyzed after therapy was discontinued and again 3 and 5 years later.

A total of 47 310 charts from patients with allergic rhinitis who received allergen immunotherapy were prescreened. The characteristics of the patients are presented in Table 1. The inclusion criteria were as follows:

1) aged between 12 and 75 years;
2) confirmed allergic rhinitis to the common allergens *D. pteronyssinus*; *D. farinae*; hazel, birch, alder, grass or mugwort; pollen; *Alternaria*; or cat;
3) intermittent or persistent allergic rhinitis according to ARIA [1] without any significant improvement after symptomatic treatment and meeting the criteria for AIT. 'Intermittent' meant that symptoms were present < 4 days a week or for < 4 consecutive weeks, and 'per-

TABLE 1. The characteristics of allergen immunotherapy applied in all studied patients

Type of allergenic extracts	The obtained mean ± SD cumulative dose (in TU per year) of AIT per patient	
	Preseasonal course	Perennial course
Allergovit grass (100%) pollen allergoid ($n = 352$)	9300 ±350^	13200 ±2650*
Allergovit birch (100%) pollen allergoid ($n = 101$)	8750 ±200	14600 ±1900^
Allergovit trees pollen (birch – 35%, hazel – 35%, alder – 30%) allergoid ($n = 108$)	5230 ±250	18100 ±2800
Allergovit mugwort (100%) allergoid ($n = 65$)	3300 ±500	12700 ±1500
Novo-Helisen Depot mites (*D. pteron*. 50%, *D. farinae* 50%) allergenic extract in depot formulation ($n = 334$)	–	68200±4500
Novo-Helisen Depot cat (100%) allergenic extract in depot formulation ($n = 55$)	–	48900 ±6700
Novo-Helisen Depot *Alternaria* (100%) allergenic extract in depot formulation ($n = 41$)	–	53500 ±3000^^

SD – standard deviation, TU – therapeutic units: demonstration of clinical efficacy and safety in clinical studies determines an appropriate dose of the product, and TUs are assigned accordingly. TUs reflect the quality and consistency of the product on the basis of a comparison with the IHRP as well as the clinical efficacy and safety (www.allergopharma); ^the mean cumulative dose of Phl p 5 is approximately 93 µg per year *the mean cumulative dose of Phl p 5 is approximately 265 µg per year ^,^^the mean cumulative dose of Alt a 1 is approximately 68 µg per year. There was no possibility of obtaining information about cumulative doses of allergens for other extracts (no product information), *n* – number of patients.

TABLE 2. The clinical characteristics of the study group

Parameter	Study group ($n = 1056$)
Age ± SD (range) of patients before AIT was started [years]	25.7 ±9.2 (12–78)
Women (%)	68
Family history of atopy (%)	612 (58)
Mean time of allergic disease duration ± SD [years]	5.2 ±3.3
Mean time of AIT ± SD [years]	3.2 ±0.8
Confirmed clinical allergy to (%):	
Grass	352 (54.6)
Trees	108 (10.2)
Birch	101 (9.6)
Mugwort	65 (6.2)
Mites	334 (31.6)
Alternaria	41 (3.9)
Cat	55 (5.2)
Intermitten allergic rhinitis (%)	748 (70.9)
Persistent allergic rhinitis (%)	473 (29.1)

SD – standard deviation.

sistent' meant that symptoms were present more than 4 days a week and for more than 4 consecutive weeks.

Additionally, allergic rhinitis was classified as seasonal allergic rhinitis (SAR) if symptoms were induced by exposure to pollen or *Alternaria* allergens and as perennial allergic rhinitis (PAR) if symptoms were induced by mites or cat exposure. The classification of SAR and PAR was used in the final assessment of patients:

1) completion of three years of preseasonal or perennial mono SCIT for a single allergen mentioned above. The details are presented in Table 1;
2) lack of other chronic diseases;
3) consent to data publication.

The exclusion criteria were lack of completion of AIT; polysensitization and SCIT to more than one group of allergens; lack of consent; and lack of complete therapy documentation.

From the databases, 2355 patients were identified after prescreening, and 1056 were randomly selected for further analysis.

The following patient data were analyzed:

1) The medical history of allergic diseases with a confirmed diagnosis.
2) The results of skin prick tests with inhalant allergens: *D. pteronyssinus*; *D. farinae*; pollen from grass, birch, hazel, alder, or mugwort; *Alternaria*; and cat. A positive result of the test was based on the presence of wheals of

3 mm or greater in diameter and concomitant wheals with histamine of 5 mm or greater in diameter [7, 8].

3) The results of assays for IgE and IgG4 against the allergens mentioned above (uni-CAP, Thermo Fisher, Sweden).
4) The combined symptom medication score (SMS) at baseline, after a 3-year course of SCIT and again 3 and 5 years later. In the medical databases, we analyzed daily symptom scores based on the patient's recorded clinical symptoms, which were monitored during SCIT, and symptomatic treatment during the allergen exposure period. Patients with SAR filled in the paper diary during the pollen season: for trees (birch) from January to May, for grass from May to July, for mugwort from June to August, and for *Alternaria* from May to September. Patients with PAR and allergies to mites filled in the same type of a paper diary from September to March and for the whole year for in the case of an allergy to cats. Patients completed a diary every day during the appropriate period of allergen exposure. The data, including symptoms and medication use, were averaged monthly and presented with the standard deviation. The obtained data were compared between baseline, the end of AIT, and 3 and 5 years after AIT was discontinued. The severity of ocular (VAS eye) and nasal symptoms (VAS nose) was recorded using a VAS scale of 100 mm. Eye and nose symptoms were categorized as 'mild' (VAS > 0 but ≤ 30 mm: 1 point), 'moderate' (VAS: > 30 mm and ≤ 70 mm: 2 points), or 'severe' (VAS > 70 mm: 3 points) [9]; all monthly mean scores for eye and nose symptoms were summarized for further analysis. The patients recorded the use of medications during the same period as that in which symptoms were monitored on their diary cards, and every day a score was assigned (1 point: used only nasal corticosteroids or eye drops for a minimum of 1 day per week; 2 points: the previous therapy plus a minimum of one tablet of levocetirizine per day; 3 points: the previous therapies plus a minimum of one 4 mg tablet of methylprednisolone per day). The SMS was calculated for each patient based on the mean monthly results of the symptom scores and medication use. The SMS calculation was performed before and after SCIT as mentioned above. All monitoring procedures were performed as part of a multiannual program for monitoring allergy symptoms [9].
5) The results of the rhinitis symptom score (RSS) and the rhinoconjunctivitis quality of life (RQLQ) questionnaires [10]. The questionnaires were administered before SCIT, after SCIT and 3 and 5 years later. The rhinitis symptom score was adapted from a 31-item symptom scale validated in patients with rhinoconjunctivitis [11].

The efficacy of therapy was assessed based on the criterion of a minimum of 20% improvement (according to the recommendations of the European Academy of Allergy and Clinical Immunology) of all parameters at the same time. The SMS, RSS, and RQLQ were compared between the start and the end of treatment and after treatment (3–5 years later).

The study was approved by the local ethics committees of the Medical University of Silesia in Katowice, Poland (KNW/0022/KB/I/12/18). All patients signed an informed consent form for all procedures and gave consent to data publication.

STATISTICAL ANALYSIS

The statistical analysis was performed using Statistica version 8.12 (SoftPOl, Poland). Descriptive analyses were performed. Student's *t*-test for unpaired data was used to analyze differences in medication and symptom scores. ANOVA or the Wilcoxon test was used to analyze other differences between groups.

Univariate and multivariate analyses were performed. First, independent variables were analyzed in the univariate analysis, and predictors of good responses to SCIT were determined. The following parameters were taken into consideration: sex, age, type of allergic rhinitis, smoking, family history of atopy, monosensitization, concomitant asthma, concomitant atopic dermatitis, type of allergen (allergen), mean duration of disease before treatment, educational status, mean duration of treatment, type of desensitized allergen in the SCIT and preseasonal vs. perennial AIT for a pollen allergy. The odds ratio (OR) was calculated for predictors. In the second step, a multivariate analysis was performed. A logistic regression model was calculated for the parameters as described above. Then, the most predictive regression model was presented. The differences were considered significant at $p < 0.05$.

RESULTS

In the final analysis, 806 (76.3%) patients met the criterion of 20% or more improvement of all analyzed parameters after SCIT, regardless of the desensitized allergen. In 250 (23.7%) patients, there was no significant effect or lack of effect. A total of 109 (10.3%) patients did not have improvement in SMS, RSS and RQLQ scores after SCIT. Further, 91 (8.6%) patients did not have improvement in SMS and RSS scores but did experience a positive treatment effect based on RQLQ. There were 27 (2.6%) patients with improvement only in the SMS score, 18 (1.7%) only in the RSS score and 5 (0.5%) only in the SMS and RQLQ scores. No other possibilities were obtained. The detailed changes of the analyzed parameters are presented in Table 3. Most

TABLE 3. The changes in analyzed parameters just after AIT relative to those at baseline for patients with a minimum 20% improvement in all analyzed parameters

Allergens and type of AIT ($n = 806$)	Mean changes in parameters just after AIT relative to those at baseline				
	SMS (Δ%)	RSS (Δ%)	RQLQ (Δ%)	LS mean specific IgE	LS mean specific IgG4
Grass pollen ($n = 293$):					
Perennial AIT ($n = 202$)	3.2 ±1.6 (76)	2.9 ±1.8 (82)	0.8 ±0.4 (79)	−1.9 ±0.8	2.8 ±1.5
Seasonal AIT ($n = 91$)	1.9 ±0.9 (54)	1.1 ±0.5 (69)	0.5 ±0.2 (66)	−1.7 ±0.6	2.2 ±0.9
Trees pollen ($n = 90$):					
Perennial AIT ($n = 49$)	2.8 ±1.5 (71)	3.2 ±1.9 (79)	1.1 ±0.9 (66)	−2.3 ±1.2	3.8 ±2.1
Seasonal AIT ($n = 41$)	2.1 ±1.7 (62)	2.2 ±1.5 (55)	1.2 ±0.8 (69)	−1.9 ±0.8	3.2 ±2.4
Birch ($n = 82$):					
Perennial AIT ($n = 59$)	3.2 ±1.6 (76)	2.9 ±1.8 (82)	0.8 ±0.4 (79)	−1.9 ±0.8	2.8 ±1.5
Seasonal AIT ($n = 23$)	1.9 ±0.9 (54)	1.1 ±0.5 (69)	0.5 ±0.2 (66	−1.7 ±0.6	2.2 ±0.9
Mugwort ($n = 38$):					
Perennial AIT ($n = 21$)	3.2 ±1.6 (76)	2.9 ±1.8 (82)	0.8 ±0.4 (79)	−1.9 ±0.8	2.8 ±1.5
Seasonal AIT ($n = 17$)	1.9 ±0.9 (54)	1.1 ±0.5 (69)	0.5 ±0.2 (66)	−1.7 ±0.6	2.2 ±0.9
House dust mites ($n = 255$)	3.2 ±1.6 (76)	1.1 ±0.5 (69)	4.6 ±0.7	−1.7 ±0.6	−1.7 ±0.6
Alternaria ($n = 19$)	3.2 ±1.6 (76)	5.3 ±2.8	5.1 ±1.9	−1.7 ±0.6	−1.7 ±0.6
Cat ($n = 29$)	3.2 ±1.6 (76)	2.2 ±1.6	4.8 ±1.2	−1.7 ±0.6	−1.7 ±0.6

SMS – combined symptom medication score, RSS – results of the rhinitis symptom score questionnaire, RQLQ – results of the rhinoconjunctivitis quality of life questionnaire, ^least square (LS) mean of the change between the concentration of specific IgE (IgG4) for any allergen for which SCIT was performed at the start of therapy and after completion of therapy.

of the patients reported a subjective lack of significant difference between nasal symptoms before and after AIT.

The majority of analyzed patients experienced significant improvement after SCIT, according to the inclusion criteria. Improvements were seen after SCIT for grass in 241 (83.2%) participants, after AIT for birch in 82 (81.2%) participants and after SCIT for mites in 255 (76.4%) participants, and less improvement was seen for trees and mugwort in 38 (58%) participants and for *Alternaria* (46.3%). There were no significant differences in effectiveness between seasonal or perennial SCIT for birch ($p = 0.21$), but perennial SCIT for grass was more effective than preseasonal SCIT for grass ($p = 0.04$).

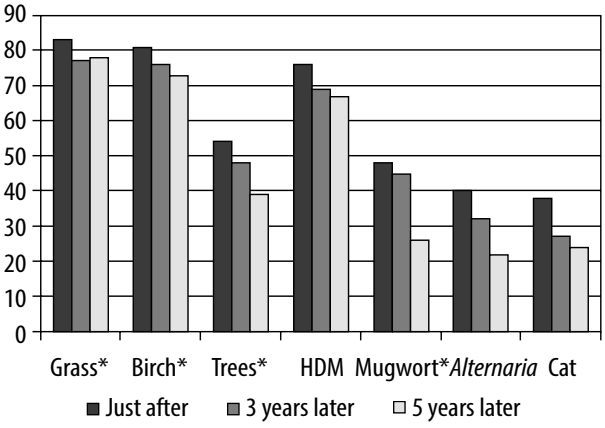

FIGURE 1. Long-term effect (3 and 5 years) of SCIT according to the type of allergen

*The effect after perennial or seasonal SCIT, HDM – house dust mites; just after – analysis of the percentage of responders just after SCIT concluded, 3 years later – the analysis 3 years after SCIT ended; 5 years later – the analysis 5 years after SCIT ended. There was a significant decrease in the effect of SCIT to trees, mugwort, *Alternaria* (also after 3 years) and cat (also after 3 years) after 5 years of observation ($p < 0.05$).

The long-term (3-year follow-up) effect of perennial SCIT for grass pollen, birch, tree and mites as well as that of seasonal SCIT for birch was observed in most patients. However, there was a decrease in efficacy in the extended 5-year follow-up after SCIT, especially for patients who received SCIT for mugwort, *Alternaria* and trees. The detailed data are presented in Figure 1.

Univariate analysis for the association of the response definition (≥ 20% improvement) after SCIT with independent variables.

Statistically significant predictors of a better treatment outcome were short disease duration (OR = 3.56); high level of education (OR = 2.81); SCIT for grass pollen (OR = 2.78, $p < 0.05$), birch (OR = 2.22, $p < 0.05$), and house dust mites (OR = 2.16); and the presence of intermittent allergic rhinitis before SCIT (OR = 2.04). The detailed data are presented in Table 4.

Multivariate analysis for responders (defined as patients with ≥ 20% improvement according to the inclusion criteria).

Statistically significant predictors of a better treatment outcome were SCIT for grass pollen (OR = 2.34, β coefficient = 0.602, p = 0.035), SCIT for birch (OR = 2.25, β coefficient = 0.712, p = 0.021) and only intermittent allergic rhinitis before SCIT (OR = 2.05, β coefficient = 0.615, p = 0.039).

DISCUSSION

The results obtained in this study revealed the importance of allergen immunotherapy. Most patients benefitted from the therapy. The results herein are comparable with many observations and guidelines [2, 4, 12]. More than 75% of the studied patients responded to the therapy; however, the inclusion criteria of > 20% improvement recommended by the EAACI that were used were not overly restrictive [13]. The Mailing's criteria of > 30% improvement in all analyzed parameters simultaneously (SMS, RSS RQLQ) after AIT were achieved by 71% of the analyzed patients (not published in this study). However, a significant number of people did not meet the improvement criteria despite their correctly meeting the inclusion for SCIT. This problem has been observed and discussed in some publications and recommendations [14, 15].

In the present study, the first key to obtaining good SCIT results was the type of allergen to which the patient was desensitized. The positive response to immunotherapy for grass or birch pollen is consistent with many published studies [4, 16]. Similarly, a good response to house dust mite SCIT has also been previously confirmed [4, 17]. However, the relatively poor effect of SCIT for mugwort, *Alternaria* or cat allergies, especially in long-term observations, is important and novel information. The evidence of a worse effect after SCIT for *Alternaria* compared to that after SCIT for other allergens has been previously emphasized [18]. The group with a significant lack of response to SCIT for mugwort and the rapid decrease in the effect requires further investigation. It is very important to address whether this type of immunotherapy is a valuable treatment method for patients with allergic rhinitis.

Immunotherapy for cat allergens remains a problem. Previous trials have presented a wide range of efficacies, and the results obtained herein are within the published range. However, a new method of AIT is still being developed [19, 20].

Among the predictors of good responses to SCIT, educational status was confirmed. Patients who were highly educated had better SCIT results than patients with a low education level. In the literature, short disease duration prior to SCIT and the presence of intermittent allergic rhinitis are known to be predictors of AIT efficacy [4, 14]. However, in the multivariate analysis, the variable short disease duration did not play an important role. In contrast to many guidelines and studies that recommend starting allergen immunotherapy in the early phase of allergic disease, some trials show that the benefits of AIT are also possible to achieve when SCIT is administered to patients with prolonged allergic rhinitis [12].

Some of the variables did not play a significant role as predictors of responsiveness to SCIT, for example, for

TABLE 4. Predictors of responses to SCIT based on the univariate analysis for individuals with > 20% improvement according to the inclusion criteria

Independent variable	OR for achieving > 20% improvement	*P*-value
Age (< 35 vs. > 35 years)	0.88	0.502
Sex (female vs. male)	1.02	0.872
Education (high vs. low level)	2.81	0.018
Smoking (yes vs. no)	1.12	0.772
Persistent allergic rhinitis (yes vs. no)	1.55	0.231
Intermittent allergic rhinitis (yes vs. no)	2.04	0.025
Concomitant asthma (yes vs. no)	0.98	0.221
Concomitant atopic dermatitis (yes vs. no)	0.79	0.061
Atopy in family (yes vs. no)	1.03	0.866
Short duration of allergic disease before SCIT (< 5 vs. > 5 years)	3.56	0.009
SCIT for grass pollen (yes vs. no)	2.78	0.014
SCIT for birch pollen (yes vs. no)	2.22	0.024
SCIT for mugwort (yes vs. no)	1.19	0.731
SCIT for HDM (yes vs. no)	2.16	0.031
SCIT for *Alternaria* (yes vs. no)	1.13	0.788
SCIT for cat (yes vs. no)	1.39	0.907
SCIT for trees (yes vs. no)	1.66	0.082
LS mean specific IgE	1.59	0.072
LS mean specific IgG4	1.88	0.056
Seasonal vs. perennial SCIT	1.54	0.076
Monosensitization before SCIT (yes vs. no)	1.11	0.542
Duration of SCIT – 3 vs. 5 years (preseasonal or perennial)	0.89	0.087

SCIT – subcutaneous injection allergen immunotherapy, HDM – house dust mites.

patients with allergies and monosensitization. In particular, changes in IgG4 were not good predictors of responsiveness; however, the odds ratio was on the border of statistical significance. It seems that this outcome is further evidence that polysensitized patients should be considered for this type of treatment. A similar opinion was presented in the EAACI recommendation [4].

It is very interesting that the protocol of the therapy (seasonal or perennial) did not have a significant impact on the final results of SCIT for grass or birch pollen. Only a few studies have analyzed this problem. There is currently a view that SCIT is most effective for perennial therapy. However, the observations in most of these trials concluded one or three years after immunotherapy was discontinued [4].

The SCIT duration variable, based on a 3- or 5-year course of therapy, was not a significant predictor of responsiveness. This finding is consistent with other observations [12].

The main limitation of the study is that it was a retrospective observation study based on a protocol that was proposed many years after the treatment had ended. Therefore, the inclusion of other parameters to assess efficacy was limited.

The criterion of a > 20% improvement after treatment, despite the EAACI recommendation, seems to be insufficient to assess responders and nonresponders to therapy. We decided to increase the restrictiveness of the criterion and to use this percentage for all analyzed parameters as a cut-off for responders. Further observations are important.

CONCLUSIONS

Based on these observations and data analyses, the best predictors of responsiveness to SCIT are the presence of intermittent allergic rhinitis to grass or birch pollen. Patients with allergies to house dust mites and persistent allergic rhinitis had slightly worse results than patients with intermittent grass or birch pollen allergies. Patients with allergies to mugwort, *Alternaria* or cat can have poor responses to SCIT, especially in the long-term follow-up. New prospective trials on the long-term effects of AIT are awaited.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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